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Treatment with Fludarabine for Patients with Follicular and other Low Grade Non-Hodgkin's Lymphoma and Waldenstrom's Macroglobulinemia Practice Guideline Report #6-2

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SUMMARY

Guideline Questions

1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom's Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations.
2. What are the toxicities of fludarabine?

Target Population

These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom's Macroglobulinemia who require therapy. Patients who require initial therapy, or who have been previously treated, are considered.

Recommendations

Previously Untreated Patients with Stage III-IV Low Grade Lymphoma

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection, and outcomes of interest.

Previously Treated Patients with Stage III-IV Low Grade Lymphoma

- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection, and outcomes of interest.

Patients with Waldenstrom's Macroglobulinemia

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.

- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Qualifying Statements

- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine, and prednisone, fludarabine significantly depresses T-cell-mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.
- Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
- The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.
- Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Methods

Entries to MEDLINE (1985 through June 2001), CANCERLIT (1985 through March 2001), and Cochrane Library (1999 through Issue 2, 2001) databases and abstracts published in the proceedings of the annual meetings of the American Society of Hematology (1997-2000) and the American Society of Clinical Oncology (1997-2001) were systematically searched for evidence relevant to this practice guideline report. In addition, the Physician's Data Query clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and PUBMED were searched.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Hematology Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Hematology Disease Site Group, which is comprised of hematologists, medical oncologists, radiation oncologists, methodologists, and a patient representative.

External review by Ontario practitioners for all reports was obtained through a mailed survey. Final approval of all reports was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, teniposide, and prednisolone, plus interferon, in a randomized trial involving 131 previously untreated patients ages 60-75 years, with follicular lymphoma and at least one high-risk feature. Patients receiving fludarabine had an inferior two-year time to treatment failure (49% versus 63%, p<0.05) and two-year survival (62% versus 77%, p<0.05).
- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 309 previously untreated patients with diffuse small lymphocytic and follicular small cleaved or mixed cell lymphoma. Respective median progression-free survivals were 494 and 396

days (p value not given). Too few events had occurred to allow for an assessment of overall survival.

- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients receiving fludarabine had a superior two-year progression-free (32% versus 14%; p=0.028) and two-year treatment-free survival (41% versus 20%; p=0.034). No difference in two-year overall survival was detected (70% versus 75%; p=0.738). This study also assessed quality of life and demonstrated superior social function in patients receiving fludarabine.
- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, and prednisone in a randomized trial reported in preliminary abstract form involving 92 patients with Waldenstrom's Macroglobulinemia who were either refractory to or relapsed from initial alkylator-based therapy. Response was superior in patients receiving fludarabine (28% versus 11%; p=0.019). Superior progression-free survival in responding patients (p=0.02) and treatment-free survival in all patients (p=0.04) were also observed with fludarabine. No difference in survival was detected. Fludarabine was associated with less mucositis and alopecia; no differences in other toxicities were detected. Using a Q-TWiST analysis, patients receiving fludarabine spent more time without symptoms of disease or treatment toxicity (5.9 months; p=0.006).

Related Guidelines

The Practice Guidelines Initiative's:

- Practice Guideline Report #6-1: *Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia*.
- Evidence Summary Report #6-8: *Rituximab in Lymphoma*.

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*The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*

Visit http://www.cancercare.on.ca/access_PEBC.htm for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:

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FULL REPORT

I. QUESTIONS

1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom's Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations.
2. What are the toxicities of fludarabine?

II. CHOICE OF TOPIC AND RATIONALE

Three hundred and fifty to 500 new cases of follicular and other low grade non-Hodgkin's lymphoma are diagnosed in Ontario each year. This condition, while usually indolent, is not considered curable with currently available therapies. Treatment is aimed at controlling symptoms and prolonging survival. Options include observation, local radiotherapy, and oral chemotherapy with chlorambucil, prednisone, or more aggressive regimens that include cyclophosphamide, vincristine, and prednisone (CVP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Recent advances include the development of new agents that are active against lymphoma, including the purine analogues (fludarabine, cladribine) and monoclonal antibodies (rituximab). Although these agents show encouraging response rates in phase II trials, algorithms for treating patients with low grade lymphoma have not been clearly defined.

In 1994, the Hematology Disease Site Group (Hematology DSG) was asked by the Systemic Treatment Committee of Cancer Care Ontario (formerly the Ontario Cancer Treatment and Research Foundation) to consider developing guidelines for using fludarabine when treating patients with chronic lymphocytic leukemia (CLL) and lymphoma. This topic was considered as a potential priority because of uncertainties about the role of fludarabine in treating these conditions, observed variation in practice across Ontario, and high drug-acquisition costs. A practice guideline assessing the role of fludarabine in treating patients with CLL was completed (Practice Guidelines Initiative Practice Guideline Report #6-1: *Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia*; http://www.cancercare.on.ca/access_1101.htm).

An initial draft of a guideline addressing the role of fludarabine in treating lymphoma was completed in 1995. At that time, studies testing fludarabine in lymphoma were all phase II design and restricted their assessments to response as the only clinical outcome. The DSG concluded that these data were insufficient to support a role for fludarabine as standard therapy for patients with lymphoma. This draft recommendation met with a low approval rating (58%) when circulated for practitioner feedback. Rather than attempting to redraft the guideline, the DSG elected to defer further consideration of this topic until the results of randomized trials became available. With the publication of randomized trials that assess progression-free and overall survival, and quality of life, this guideline has been re-evaluated.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by two members of the PGI's Hematology DSG and methodologists. Members of the Hematology DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on fludarabine, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered.

The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

An initial literature search was conducted in February 2000 and included the following databases: MEDLINE (1985 to February 2000), CANCELIT (1985 to January 2000), and the Cochrane Library (Issue 4, 1999). The following terms were used for MEDLINE and CANCELIT: “exp lymphoma”: (Medical subject heading (MeSH), title) combined with “fludara:” (title) or “fludarabine” (text word). The results were limited to human and English language. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), PUBMED, and conference proceedings of the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) published in 1997-1999 were searched for reports of new or on going trials. Reference lists from relevant articles were searched for additional trials.

An updated literature search of the MEDLINE (March 2000 to June 2001) and CANCELIT (March 2000 to March 2001) databases was conducted in June 2001. This update also included searches of the Cochrane Library (Issue 2, 2001), PDQ, and the 2000 ASH and 2000-2001 ASCO conference proceedings.

These same sources were searched to locate studies evaluating the role of fludarabine in Waldenstrom’s Macroglobulinemia. The search terms used in MEDLINE (1985 to June 2001) and CANCELIT (1975 to March 2001) were: “exp waldenstrom macroglobulinemia”: (MeSH and title) combined with “fludara:” (title) or “fludarabine” (text word). The search was limited to human and English language. In addition to the 2000 ASH and 2000-2001 ASCO conference proceedings, the 1997-1999 proceedings were also searched for Waldenstrom’s Macroglobulinemia.

Article Assessment

Abstracts of relevant articles obtained from the February 2000 systematic literature search were blinded for author, institution, and whether the results were positive or negative. Two reviewers then independently assessed the blinded papers for inclusion. Reviewers were also unaware of whether the studies were published in journal or in abstract form. A Kappa of 0.7 or greater was predetermined to be acceptable. Where there was a discrepancy between the reviewers’ opinions, the reviewers discussed the individual blinded studies and decided whether to include or exclude the paper based on the preset inclusion criteria. The lead author of this guideline determined the eligibility of citations identified with the updated literature search of June 2001.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were one of the following:

1. Randomized controlled trials comparing fludarabine either as monotherapy or in combination with other treatment alternatives in patients with low grade lymphoma or Waldenstrom’s Macroglobulinemia. Primary outcomes of interest included survival, progression-free survival, or quality of life.

2. Reports of fludarabine-related toxicity in patients with low grade lymphoma or Waldenstrom's Macroglobulinemia.
3. Economic evaluations comparing fludarabine to other treatment alternatives in patients with low grade lymphoma or Waldenstrom's Macroglobulinemia.

Exclusion Criteria

1. Trials of less than 10 patients (but individual case reports of toxicity were included).
2. Trials including fludarabine as part of a high-dose chemotherapy and/or transplant protocol.

Synthesizing the Evidence

Due to the heterogeneity of the treatment regimens compared with fludarabine, the varied use of fludarabine as either a single agent or as part of a combination regimen, and the lack of consistency in reporting the outcomes of interest, there was no attempt to pool efficacy data. Treatment-related toxicity data were summarized in the Adverse Events section of this document.

IV. RESULTS

Literature Search Results

A total of 151 citations were identified from the initial systematic literature search of February 2000, including 25 citations from the 1997-1999 conference proceedings. These citations were blinded with respect to author, site of work, citation, and results and were then independently reviewed by two members of the Hematology DSG. From these citations, 46 articles were considered to be potentially eligible for inclusion and were retrieved. The level of agreement by the Kappa statistic was 0.73. After further review of these 46 articles, 23 publications were assessed as meeting the eligibility criteria and included six randomized controlled trials (2-7), three economic evaluations (8-10), one quality of life analysis (11), and 13 toxicity reports (12-24). Of the six randomized controlled trials, four assessed previously untreated lymphoma patients (2-5), one assessed previously treated lymphoma patients (6), and one assessed patients with previously treated Waldenstrom's Macroglobulinemia (7).

The updated search of June 2001 identified an additional seven citations: three randomized controlled trials (25-27), two in previously untreated lymphoma patients (25,26) and one in previously treated lymphoma patients (27); one update reporting quality of life outcomes in a randomized trial assessing previously treated patients with Waldenstrom's Macroglobulinemia (28); one economic analysis (29); and two toxicity reports (30,31).

Previously Untreated Patients with Low Grade Lymphoma

Six trials addressing fludarabine in previously untreated lymphoma patients (2-5,25,26) are included in Table 1. Two trials are restricted to older patients (2,4). Two are published in article form (2,5), and four are in abstract form (3,4,25,26).

Coiffier et al (2) reported the results of a randomized trial comparing fludarabine with cyclophosphamide, doxorubicin, teniposide, and prednisone plus interferon (CHVP-IFN) in 131 patients aged 60-75 years, with follicular lymphoma, and at least one high-risk feature. Risk factors included B symptoms (fever, night sweats, and/or weight loss), an Eastern Cooperative Oncology Group (ECOG) performance status greater than 1, an increase in the serum lactate dehydrogenase (LDH) or β_2 microglobulin level, or a specific criterion measure referred to as a high tumour mass. A high tumour mass was defined as a mass greater than 7 cm, large splenomegaly, the presence of an effusion, or a compressive tumour mass. Patients receiving fludarabine had an inferior two-year time to treatment failure (49% versus [vs.] 63%, $p < 0.05$) and two-year survival (62% vs. 77%, $p < 0.05$). Using the World Health Organization (WHO) Toxicity Scale, patients receiving CHVP-IFN experienced more grade 3-4 neutropenia. No differences were detected in episodes of infection. Patients receiving CHVP-IFN experienced

more fatigue; 39% of patients receiving IFN either discontinued the drug or had dose modifications because of toxic reactions.

Table 1. Studies of previously untreated patients.

Author (report)	Number	Patient Eligibility	Fludarabine Arm	Control Arm	Progression –Free Survival*	Overall Survival*
Coiffer (2) (article)	131	Follicular lymphoma; Ages 60-75yrs., High risk disease†	Fludarabine: 25mg/m ² /day x5days q28days x 6 cycles followed by 20mg/m ² q2mos. x 6 cycles	CHVP: q28days x 6 cycles followed by q2mos. x 6 cycles; IFN 5 MU tiw x 18 mos.	FFS at 2 yrs.: 49% vs. 63% (p < 0.05)	at 2 yrs.: 62% vs. 77% (p < 0.05)
Hagenbeek (3) (abstract)	381	Low grade lymphoma; Stage III and IV	Fludarabine: 25mg/m ² /day x5days q28days x 8 cycles	CVP: q28days x 8 cycles	Median: 494 vs. 396 days (p not stated)	Not reported
Foussard (4) (abstract)	100	Low grade lymphoma; Ages 55-75 yrs. Stage II bulky II, III-IV High risk disease‡	Fludarabine: 20mg/m ² /day x 5days + Mitoxantrone 10mg/m ² x 1day each q28days x6 cycles followed by q2mos. x 3 cycles	CHEP: q28days x 6 cycles followed by q2mos. x 3 cycles	Not reported	Not reported
Zinzani (5) (article)	199	Low grade lymphoma; Stage II - IV	Fludarabine: 25mg/m ² /day x5days q28days x 6cycles	FI: q28 days x 6 cycles	at 36 mos.§: 56% vs. 90.5% (p=0.012)	at 42 mos.: 72.6% vs. 72.2% (p=ns)
Tsimberidou (25) (abstract)	159	Indolent lymphoma Stage IV	FND: x 8 cycles + IFN/dex. x1year	ATT: x 12 cycles + IFN/dex x 1 year	At 5yrs.: 45% vs. 56% p=0.01	at 5 yrs.: 83% vs. 81% (p=ns)
Bilgir (26) (abstract)	40	Low and intermediate grade lymphoma	Dose and schedule not stated	CHOP: schedule not stated	Not reported	Not reported

ATT=Alternating triple therapy; CHEP=cyclophosphamide, doxorubicin, vindesine, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP=cyclophosphamide, doxorubicin, teniposide, prednisone; CVP=cyclophosphamide, vincristine, prednisone; FFS=failure-free survival; FI=fludarabine, idarubicin; FND=fludarabine, mitoxantrone (Novantrone ®), dexamethasone; IFN=interferon; IFN/dex=interferon, dexamethasone; mos.=months; MU=million units; ns=not significant; q=every; tiw=three times per week; yrs.=years.

* Order of data provided is fludarabine vs. control arm

† High risk included any of B symptoms, ECOG performance status >1, increased LDH or β₂ microglobulin, or high tumour mass

‡ High risk factors not stated

§ Progression-free survival reported only for responding patients

Hagenbeek et al reported in abstract form (3) the preliminary results of a randomized trial comparing fludarabine with CVP in 309 patients with diffuse small lymphocytic and follicular

small cleaved or mixed cell lymphoma. Patients were stratified according to whether they needed therapy immediately upon diagnosis or had been previously observed off therapy. The dose of cyclophosphamide in patients receiving CVP was 750 mg/m² given intravenously. From an initial cohort of 381 patients, 72 (19%) were excluded after a central pathology review. The median progression-free survival was 494 days for patients receiving fludarabine and 396 days in those receiving CVP (p value not given). Too few events had occurred to allow for an assessment of overall survival. No differences in outcomes were detected when comparing subgroups of patients requiring initial therapy immediately after diagnosis and those who had been initially observed. Using the WHO Toxicity Scale, grade 2 or greater granulocytopenia and thrombocytopenia were more frequent in patients receiving fludarabine (p=0.001); significant alopecia occurred in the CVP group only.

Foussard et al reported in abstract form (4) the preliminary results of a randomized trial comparing fludarabine plus mitoxantrone (FM) with cyclophosphamide, doxorubicin, vindesine, and prednisone (CHEP) in 100 patients with low grade (excluding mantle cell) lymphoma. Eligible patients were 55-75 years of age with bulky stage II or stage III-IV disease and at least one high risk factor (not defined). Response to therapy was the only outcome reported, and only 68% of the patients accrued were evaluable for this endpoint. At one year, the response rate was superior in patients receiving FM (84% vs. 48%; p=0.023) with more complete responses (44% vs. 22%; p not indicated) apparent. Comparative toxicities were not described.

Zinzani et al (5) reported the results of a randomized trial comparing fludarabine with fludarabine plus idarubicin (FI) in 199 patients ages 25-65 years with low grade, including mantle cell, lymphoma. No differences in the respective response rates (84% vs. 81%) or survival at 42 months (73% vs. 72%) were detected (p values not given). Progression-free survival of all patients was not reported; the three-year progression-free survival in patients demonstrating a response to therapy was 90.5% in the FI group and 56% with fludarabine (p=0.012).

Tsimberidou et al reported in abstract form (25) the preliminary results of a randomized trial comparing fludarabine, mitoxantrone (Novantrone®), and dexamethasone (FND) with a multi-regimen combination, referred to as alternating triple therapy (ATT), in 142 patients with stage IV low grade lymphoma. Alternating triple therapy includes cyclophosphamide, doxorubicin, vincristine, dexamethasone, bleomycin, etoposide, cisplatin, cytarabine, mitoxantrone, prednisone, and procarbazine (CHOD-BLEO/ESHAP/NOPP). Eligible patients were less than 76 years of age and had documented adequate cardiac function. With a median follow-up of 56 months, five-year failure-free survival (FFS) was inferior in patients receiving FND (45% vs. 56% p=0.01); no difference in overall survival at five years was detected between FND and ATT (83% vs. 81%, respectively). There was more grade III-IV toxicity with ATT, including more frequent neutropenia (94% vs. 81%), thrombocytopenia (78% vs. 12%), and incidence of infection (27% vs. 12%).

Bilgir et al reported in abstract form (26) the preliminary results of a randomized trial comparing fludarabine with CHOP in patients with low and intermediate grade non-Hodgkin's lymphoma. There were 20 patients in each arm and response to therapy was the only outcome reported. Comparative toxicities were not described. Although a randomized trial, the outcomes reported were not sufficient for further consideration in this guideline.

Previously Treated Patients with Low Grade Lymphoma

Two of the three trials summarized in Table 2 evaluated fludarabine in previously treated patients with lymphoma (6,27).

Klasa et al reported in abstract form (6) preliminary results of a randomized trial comparing fludarabine with CVP in 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients were required to have had a response to all previous treatment courses; the dose of cyclophosphamide in patients allocated to CVP was

750 mg/m² given intravenously. Patients receiving fludarabine had a superior two-year progression-free survival (32% vs. 14%; p=0.028). The trial also assessed the time interval to requiring subsequent therapy (two-year treatment-free survival) and found this time was longer in the fludarabine group (41% vs. 20%; p=0.034). No difference in two-year survival was detected (70% vs. 75%; p=0.738). Patients receiving CVP experienced more nausea, vomiting, neurotoxicity, and alopecia. Patients receiving fludarabine experienced more infections; there were three treatment-related deaths in the fludarabine group but none attributed to treatment toxicity in patients receiving CVP. Quality-of-life outcomes assessed in this study were reported in a separate abstract (11), with superior social function observed in patients receiving fludarabine; no difference in other domains was detected. The authors attributed the improvement in social function to the lower incidence of nausea, vomiting, and alopecia in patients receiving fludarabine.

Tondini et al (27) reported the results of a randomized phase II trial comparing fludarabine with another purine analogue, cladribine, in 60 patients with relapsed or refractory low grade lymphoma. Responses were observed in 68% of patients receiving fludarabine and 72% of those receiving cladribine (p not given). The three-year progression-free survival in responding patients was 58% with fludarabine and 52% with cladribine (p not given). Cladribine was associated with a trend toward greater grade 3-4 neutropenia (66% vs. 50%; p not given) and more grade 3-4 thrombocytopenia (22% vs. 4%; p=0.05); the toxicity grading system was not defined. The authors concluded that both drugs were active, and that, given the observed myelosuppression, other doses and schedules of cladribine should be tested.

Table 2. Studies of previously treated patients.

Author (report)	Patient Number	Patient Eligibility	Fludarabine Arm	Control Arm	Progression-Free Survival*	Overall Survival*
Klasa (6) (abstract)	91	Low grade lymphoma; 1-4 prior regimens with response to all previous therapy	Fludarabine: 25mg/m ² /day x 5 days q28days x 8 cycles	CVP: q21days x 4-10 cycles	at 2 yrs.: 32% vs. 14% (p=0.028)	at 2 yrs.: 70% vs. 75% (p=0.738)
Tondini (27) (article)	60	Diffuse small lymphocytic or follicular lymphoma; Relapsed or refractory to previous therapy	Fludarabine: 25mg/m ² /day x 5 days q 1 mos.	Cladribine: 0.14mg/kg/day x 5 days q 1 mos.	At 3 yrs.: 58% vs. 52% † (p not stated)	Not reported
Leblond (7) (abstract)	90	Waldenstrom's Macroglobulinemia; Relapsed or refractory to alkylator therapy	Fludarabine: 25mg/m ² /day x 5 days q28days x6 cycles	CAP: x 6 cycles	Superior in fludarabine group† (p < 0.05; data not stated)	Data not stated (p > 0.05)

CAP=cyclophosphamide, doxorubicin (Adriamycin®), prednisone; CVP=cyclophosphamide, vincristine, prednisone; mos.=months q=every; yrs.=years

* Order of data provided is fludarabine vs. control arm

† Progression-free survival reported only for responding patients

Waldenstrom's Macroglobulinemia

One trial evaluating fludarabine in previously treated patients with Waldenstrom's Macroglobulinemia is summarized in Table 2 (7). No randomized trials involving previously untreated patients were identified.

Leblond et al reported in abstract form (7) the preliminary results of a randomized trial comparing fludarabine with cyclophosphamide, doxorubicin, and prednisone (CAP) in 92 patients with Waldenstrom's Macroglobulinemia that was either refractory to or relapsed from initial alkylator-based therapy. Response was superior in patients receiving fludarabine (28% vs. 11%; $p=0.019$). Superior progression-free survival in responding patients ($p=0.02$) and treatment-free survival in all patients ($p=0.04$) were also observed with fludarabine (data not provided). No difference in overall survival was detected (data not provided). Patients receiving CAP experienced more mucositis and alopecia; no differences in other toxicities were detected. In an updated abstract report of this study (28), the quality of life of the randomized groups was compared using 'time without disease symptoms and toxicity' (Q-TWiST) as the primary outcome measure. Patients receiving fludarabine had a mean gain of 5.9 months ($p=0.006$) of time without symptoms of disease or treatment toxicity, principally because of less time spent with relapsed disease.

Economic Evaluations

Four economic evaluations were identified and included one article (8) and three abstracts (9,10,29).

Sweetenham et al (8) reported the results of a cost-minimization analysis comparing CHOP, fludarabine, and rituximab in patients with relapsed indolent B-cell lymphoma. Costs of CHOP and fludarabine were assessed from a historical, single institution, cohort comparison; rituximab costs were assessed from a literature report of a multicentre phase II trial. Costs measured were for the acquisition of the antilymphoma medications and the management of treatment-related toxicity. The authors estimated the median costs to be £7,210 with CHOP, £10,022 with fludarabine, and £6,080 with rituximab. Response rates and median response durations were estimated to be similar across the three treatment groups. The authors suggested that the higher costs of fludarabine were due to higher drug-acquisition costs in comparison with CHOP, and greater costs in managing toxic events, in comparison with rituximab. The need to confirm these data in prospective randomized trials was stated. Hoffman LaRoche, a supplier of rituximab, sponsored this study.

Hieke and Kerrigan (9) estimated the costs of antilymphoma drug acquisition and the management of treatment-related toxicity of CVP, CHOP, and fludarabine by surveying 91 physicians from Canada, Germany, and Italy. Costs were obtained from a retrospective chart review of a single cycle of treatment for individual patients and then estimated over a median of six treatment cycles. Efficacy outcomes of therapy were not assessed. A direct comparison of the costs of each regimen was not provided. The authors concluded that the key determinants of cost were treatment schedule, therapy setting (in- vs. out-patient), and management of toxic events. Hoffman LaRoche sponsored this study.

Burchmore and Dowden (10) estimated the one-year costs of treatment in patients receiving fludarabine or rituximab. Rituximab costs were assessed from a phase II trial; fludarabine costs were estimated by considering published toxicity data. Efficacy outcomes were assumed to be similar. Costs for therapy at one year were estimated to be similar (\$13,688 with rituximab vs. \$13,121 with fludarabine). Genetech, a supplier of rituximab, sponsored this study.

Scott et al (29) estimated the costs of fludarabine and rituximab over a 13-month time period using data from 47 patients treated in Australia. A sensitivity analysis using varying estimates of in-patient needs and response was also included. The authors concluded that

costs (\$13,118 with rituximab and \$12,919 with fludarabine) would be similar if response and in-patient admission rates were similar. Sponsorship of this study was not indicated.

Adverse Effects

Eight of the nine randomized trials reviewed above provided some description of treatment-related toxicities (2-7,25,27). In addition, 14 toxicity reports (12-22,24,30,31) and one phase I/II trial (23) were reviewed. Further toxicity data and references can be found in the Adverse Effects section of Practice Guideline Report #6-1: *Fludarabine in Intermediate- and High-Risk Chronic Lymphocytic Leukemia* (http://www.cancercare.on.ca/access_1101.htm).

Hematologic

Myelosuppression is a side effect of fludarabine. Profound lymphopenia and mild to moderate neutropenia and thrombocytopenia can occur. Although myelosuppression is the most common side effect, ECOG grade 3 or greater hematologic toxicity is seen in 3.8% and 5% of treatment courses in previously untreated lymphoma patients (2,5). When compared with CVP in previously untreated lymphoma patients, fludarabine was associated with more grade III-IV granulocytopenia ($p=0.001$) and thrombocytopenia ($p=0.001$) (3). When compared with CHVP-IFN, fludarabine appeared to be associated with less grade III-IV granulocytopenia (5% vs. 26% of patients), but the size of the study did not allow this potentially clinically important difference to achieve statistical significance (2).

In comparison with CVP in previously treated patients with lymphoma (6), and CAP in previously treated patients with Waldenstrom's Macroglobulinemia (7), no differences in myelosuppression were observed.

Opportunistic infection

From the randomized trials, grade 3-4 clinical infection is observed in 1-2% of patients receiving fludarabine with no significant differences detected when compared with fludarabine plus idarubicin (5), CVP (3), or CHVP-IFN (2) in previously untreated lymphoma patients. In previously treated lymphoma patients, fludarabine was associated with more infections in comparison with CVP (6).

A retrospective case series assessing 2269 patients who received 7547 cycles of fludarabine reported a 3.2% incidence of opportunistic pulmonary infections (pneumocystis carinii pneumonia, candidiasis, mycobacterium avium intracellulare, aspergillus). Lack of prophylaxis was a predictor of the development of pneumocystis carinii pneumonia. Corticosteroid treatment before, during, or after fludarabine also increased the risk of opportunistic pulmonary infections (16). Cotrimoxazole prophylaxis for pneumocystis carinii pneumonia was included as part of the protocol in only one study (4); no cases of PCP were reported.

Autoimmune Phenomena

Autoimmune hemolytic anemia (AIHA) has been reported in as many as 7.5% of low grade lymphoma patients undergoing treatment with fludarabine (18); 50% of these patients had a history of AIHA. Unlike CLL, AIHA may correlate with disease progression in patients with low grade lymphoma (18). Because fludarabine has been reported to exacerbate or precipitate AIHA, the manufacturer considers AIHA to be a contraindication for using fludarabine (Practice Guideline Report #6-1). Autoimmune thrombocytopenia has also been reported (19).

Graft-versus-Host Disease

Transfusion-related graft-versus-host (GVH) disease has been anecdotally reported as occurring up to 11 months after treatment with fludarabine (14). The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force

recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products when these products contain viable lymphocytes (e.g., red cell or platelet concentrates) (15).

Tumour Lysis Syndrome

Although fludarabine-associated tumour lysis syndrome has been more typically described in patients with CLL, it has also been reported in low grade lymphoma (21).

Neurological

Peripheral neuropathy developed in 5 patients, all of which completely resolved within 5 weeks in one RCT (5) and was found to be more frequent with CVP in another (6). Five cases of unusual neurological illness were reported in fludarabine-treated patients with low grade non-Hodgkin's lymphoma (22). Neurological toxicity is dose limiting and the dose of fludarabine should not exceed the recommended dose (23).

Other

Nausea, vomiting, and mucositis are infrequent (5) and occur less frequently with fludarabine than with CVP (6). Fludarabine does not cause alopecia (5,6) and is not toxic to the kidneys or heart (5). Transient grade 2 hepatic toxicity has been observed (5). Individual cases of fatal fulminant myelofibrosis (12), fatal bone marrow necrosis (13), and seropositive symmetrical inflammatory polyarthritis (31) have been reported following fludarabine use in patients with indolent lymphoma. A single patient with low grade lymphoma was reported to have developed progressive epidermal necrolysis following a second cycle of fludarabine; the syndrome was successfully treated with high dose steroids, cyclophosphamide, and immunoglobulins. (20). There have been individual case reports of Guillain-Barré syndrome in a patient with Waldenstrom's Macroglobulinemia (30), fatal miliary tuberculosis in a patient with high grade lymphoma (17), and cryptococcal meningitis plus intracranial tuberculoma 18 months after completion of treatment in a patient with Waldenstrom's Macroglobulinemia (24).

V. INTERPRETIVE SUMMARY

Previously Untreated Patients with Low Grade Lymphoma

Six randomized trials testing fludarabine in previously untreated patients with follicular and other low grade lymphomas were identified. Of these, two (2,3) compared fludarabine with a well-described standard therapy in an adequate number of patients and reported important efficacy outcomes that included at least progression-free survival, and in the case of one study, overall survival (2). These two studies were therefore used in determining guideline recommendations.

The trial comparing fludarabine with CHVP-IFN (2) was conducted in older patients with high-risk disease who are generally considered to be more susceptible to treatment-related toxicity. Despite the potential concern of treating these patients with an anthracycline regimen, superior outcomes, including survival, were observed in patients receiving CHVP-IFN. This study was given proportionately more weight in comparison with other studies as it was reported in full article form and found a survival difference between treatment groups (a difference in survival is rarely seen in randomized trials assessing patients with follicular and other low grade lymphoma). Issues related to contrasting CHVP-IFN to treatment regimens commonly used in Ontario, such as CVP or CHOP, were recognized by the Hematology DSG and are considered within the section describing the DSG Consensus Process.

The study comparing fludarabine with CVP (3) in previously untreated patients was given proportionately less weight. The study results are thus far available in abstract form, have not addressed overall survival, show a difference in median progression-free survival of a relatively small magnitude (494 days vs. 396 days; p not given), and describe more hematologic toxicity in patients receiving fludarabine. In the absence of survival and more complete toxicity

data, the magnitude of the progression-free survival difference was considered to be of questionable clinical importance. This trial does, however, demonstrate that fludarabine is an active agent for patients with low grade lymphoma, a finding that contributed to how this drug was regarded when considering options in previously treated patients.

Four other trials conducted in previously untreated patients did not contribute to the DSG conclusions and recommendations. The trials comparing fludarabine with FI (5) and FND with ATT (25) did not include standard control arms and showed no difference in outcomes that would lead to the consideration of new treatment policies. The trials comparing FM with CHEP (4) and CHOP (26) did not report progression-free or overall survival, and/or did not have sufficient follow-up of randomized patients, and were thus considered too preliminary to contribute to recommendations.

Previously Treated Patients with Low Grade Lymphoma

Two randomized trials testing fludarabine in previously treated patients with follicular and other low grade lymphoma were identified (6,27). One of these compared fludarabine to a well-described standard therapy in a sufficient number of patients to assess progression-free survival and toxicity and to estimate overall survival (6).

The trial comparing fludarabine with CVP in previously treated patients (6) demonstrated superior progression-free and treatment-free survival in patients receiving fludarabine. No survival difference was detected. A quality-of-life assessment detected superior social function with no differences in other quality-of-life domains (11). These results were considered to be sufficient to recommend fludarabine as an acceptable treatment option for these patients. More complete reporting of results in article form, including a description of the baseline features of the patients, may allow for a better assessment of the time point at which fludarabine should be considered the preferred treatment option.

The trial comparing fludarabine with cladribine (27) did not contribute to the DSG conclusions and recommendations as it did not include a standard control arm.

Waldenstrom's Macroglobulinemia

One randomized trial assessing fludarabine in patients with Waldenstrom's Macroglobulinemia was identified that compared fludarabine with CAP in previously treated patients (7). The report of this trial demonstrates that fludarabine is an active agent in this disease. Although data are preliminary, fludarabine is associated with a superior response rate, at least comparable outcomes when assessing disease control, and reduced toxicity. These parameters may result in a superior quality of life in patients receiving fludarabine as reported in the preliminary, abstract report assessing quality of life using a Q-TWiST analysis (28). Fludarabine was, therefore, considered an acceptable treatment option in patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Economic Evaluations

The economic evaluations were considered to be preliminary and of a hypothesis-generating nature. These reports did not explicitly indicate the payer perspective of the analyses, did not adequately describe the process used to ensure that the competing treatment options were provided to similar patient groups, and did not include an explicit statement regarding which direct and indirect costs were measured. They appeared to be heavily weighted by the drug acquisition charges rather than by measuring costs. Treatment efficacy outcomes were either assumed to be equivalent or were not considered. Based on these limitations, these data were considered to be insufficient to contribute to conclusions and recommendations.

VI. ONGOING TRIALS

The Hematology DSG is aware of the following ongoing trial. The progress of this trial will be monitored and the reported results will be reviewed when available:

Protocol ID(s)	Title and details of trial
BNLI-MCD/FMD, EU-20035	Phase III Randomized Study of Chlorambucil, Mitoxantrone, and Dexamethasone Versus Fludarabine, Mitoxantrone, and Dexamethasone in Patients with Newly Diagnosed Stage III or IV Follicular Non-Hodgkin's Lymphoma (Summary Last Modified 09/2000)

Five hundred previously untreated patients (250 per arm), ages 18 to 70 years will be accrued for this study within four years.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Hematology DSG considered differences in survival and quality of life to be important outcomes upon which treatment recommendations could be based. The DSG also discussed the use of surrogate outcomes, such as response rate and progression-free and treatment-free survivals as proxies for overall survival and quality of life. As improved, progression-free survival may be a desirable goal for some patients and may translate into improved quality of life, it was considered to be a potentially useful outcome for determining a treatment recommendation. Treatment-free survival may also be a reasonable proxy measure for quality of life as it is assumed that disease progression necessitating therapy would be associated with clinically important symptoms, and deferring any treatment-related toxicity would be valued. However, there may be a bias in measuring this outcome, as none of the randomized trials described were blinded for treatment allocation. Knowing that patients were previously unexposed to fludarabine could favour the re-initiation of fludarabine therapy in patients previously allocated to standard therapy. Treatment-free survival was, therefore, considered in conjunction with progression-free survival in making recommendations. Response rate was felt to be an inadequate surrogate marker upon which to base a treatment recommendation and an outcome more appropriately used in trials reporting results of preliminary new drug testing. Response rate has been included in this report to assist in interpreting progression-free survival when this latter outcome has been reported only in those patients demonstrating a response.

In considering patients with previously untreated low grade lymphoma, the DSG gave greatest weight to the trial comparing fludarabine with CHVP-IFN (2). As this trial showed a difference in all efficacy outcomes, including survival, in favour of the CHVP-IFN group, it was concluded that there was insufficient evidence to support using fludarabine as initial therapy. The DSG recognized that CHVP-IFN is not considered a standard treatment in Ontario. It is generally believed that CHVP and CHOP result in similar outcomes. Furthermore, other than for the potential that more rapid responses are seen in some patients treated with CHOP, it is generally believed that CHOP and CVP produce similar outcomes. With respect to the addition of IFN to chemotherapy, the DSG is aware of the uncertainty of the role of this agent and is in the process of completing a guideline assessing IFN in patients with follicular and other low grade lymphomas. As a result, the DSG concluded that CHVP-IFN may be comparable to the standard regimens (CVP and CHOP) used in Ontario for such patients. The DSG acknowledges the potential risks of drawing these conclusions. The possibility that the risk criteria used in this study (2) may lead to the inclusion of patients with occult transformed lymphoma is also recognized. Such patients may have superior outcomes with CHVP-IFN due to treatment that includes doxorubicin. Separate studies are needed to compare fludarabine with a standard therapy in lower risk patients.

In patients with previously treated low grade lymphoma, the one randomized trial in which fludarabine was compared with a standard option (CVP) demonstrated superior progression-free and treatment-free survival and improvement in one-quality-of life domain

(social function) in patients receiving fludarabine; no difference in survival was detected (6). These data were considered sufficient to warrant a recommendation supporting the use of fludarabine as an acceptable treatment option for these patients.

The trial comparing fludarabine with CAP in patients with previously treated Waldenstrom's Macroglobulinemia showed that fludarabine was associated with superior responses, progression-free survival in responding patients and treatment-free survival in all patients, both with reduced toxicity (7). Although each of these individual outcomes would be considered as having limitations in leading to a recommendation, the sum of these findings, along with the preliminary suggestion of superior quality of life as assessed by a Q-TWiST analysis (28), resulted in the conclusion that fludarabine was an acceptable treatment option.

Finally, the DSG recognizes that the role of monoclonal antibody therapies, such as rituximab, will need to be included in any subsequent determinations of the sequence of therapies for these patients

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Hematology DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom's Macroglobulinemia who require therapy. Patients who require initial therapy, or have been previously treated, were considered.

Draft Recommendations

Previously Untreated Patients with Stage III–IV Low Grade Lymphoma

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection and outcomes of interest.

Previously Treated Patients with Stage III-IV Low Grade Lymphoma

- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection and outcomes of interest.

Patients with Waldenstrom's Macroglobulinemia

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.
- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Qualifying Statements

- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine,

and prednisone, fludarabine significantly depresses T-cell mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.

- Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
- The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.
- Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Related Guidelines

- Practice Guidelines Initiative's Practice Guideline Report #6-1: *Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia*
- Evidence Summary Report #6-8: *Rituximab in Lymphoma*.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 178 clinicians (100 medical oncologists and 78 hematologists) in Ontario. The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (second mailing of the complete package). The Hematology DSG reviewed the results of this survey.

Results

Of the 178 surveys sent, seven were excluded due to retirement or leaves, and 87 (51%) were returned. Fifty-three of these respondents (61%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice, and three additional respondents did not complete this question; 56 clinicians completed the survey. Key results of the practitioner feedback survey are summarized in Table 3.

Table 3. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.	54 (96)	2 (4)	0
There is a need for a clinical practice guideline on this topic.	53 (95)	3 (5)	0
The literature search is relevant and complete.	53 (95)	3 (5)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	54 (96)	0	2 (4)
The draft recommendations in this report are clear.	55 (98)	1 (2)	0
I agree with the draft recommendations as stated.	51 (91)	3 (5)	2 (4)
This report should be approved as a practice guideline.	48 (87)	6 (11)	1 (2)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	47 (89)	3 (5)	3 (6)

Summary of Written Comments

Nineteen respondents (34%) provided written comments regarding the content of the practice-guideline-in-progress report; seven of these indicated support for specific aspects of the report. Twelve other comments included:

1. Two physicians expressed concern regarding the appropriateness of including CHOP as an acceptable first-line treatment option; one other physician indicated that CHVP-IFN should be the treatment of choice.
2. Three physicians indicated that the recommendations are too restrictive for untreated patients and that, based on the results of phase II trials (of fludarabine alone or in combination with other agents) in previously untreated patients, phase III trials in previously treated patients, and phase III trials in patients with chronic lymphocytic leukemia, fludarabine could be recommended as a treatment option for previously untreated patients. One of these respondents noted that the recommendations vary from those used in other parts of Canada.

However, in addition to the seven comments of support, one other respondent indicated that the recommendation for use in previously untreated patients was not worded strongly enough, and suggested the recommendation should “discourage” the use of fludarabine in these patients.

3. Four respondents expressed concern regarding methodologic issues, including the use of abstracts, limiting the data reviewed to randomized trials, and basing recommendations on a small number of trials assessing a limited number of patients (e.g., Waldenstrom’s Macroglobulinemia).
4. One respondent questioned whether the use of fludarabine might be associated with an improved ability to subsequently harvest autologous stem cells for transplantation.

Modifications/Actions

1. With respect to alternative options for first-line therapy, the DSG recognizes the importance and complexity of this topic but did not intend to create evidence-based recommendations for these alternatives. The DSG agrees that there are circumstances for which first-line use of an anthracycline-containing regimen would be inappropriate but is also aware of circumstances for which this treatment would be reasonable.
2. With respect to the use of phase II data, and of phase III data involving other patient groups, the DSG considered these studies to have interpretive limitations posed by the trial designs.

The DSG concluded that recommendations should be based on the results of randomized trials assessing patients with follicular and other low grade lymphomas. This difference in guideline methodology may account for the variation in resulting recommendations between geographic regions.

3. The DSG recognizes that results from abstracts must be interpreted with caution as the information provided is incomplete and precludes the full assessment of the quality aspects of the study. Abstracts were, therefore, given less weight than published papers in forming recommendations. However, systematic reviews ideally capture the results of all published and unpublished trials to most thoroughly evaluate a topic, including the consideration of publication biases.
4. The DSG did not feel sufficient data were available to comment on the subsequent ability to harvest autologous stem cells.

Based on the above considerations, there were no changes to the draft recommendations.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology DSG and the Practice Guidelines Coordinating Committee.

Target Population

These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom's Macroglobulinemia who require therapy. Patients who require initial therapy, or who have been previously treated, were considered.

Recommendations

Previously Untreated Patients with Stage III-IV Low Grade Lymphoma

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection and outcomes of interest.

Previously Treated Patients with Stage III-IV Low Grade Lymphoma

- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection and outcomes of interest.

Patients with Waldenstrom's Macroglobulinemia

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.
- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Qualifying Statements

- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine,

and prednisone, fludarabine significantly depresses T-cell mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.

- Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
- The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.
- Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Related Guidelines

The Practice Guidelines Initiative's:

- Practice Guideline Report #6-1: *Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia*.
- Evidence Summary Report #6-8: *Rituximab in Lymphoma*.

X. JOURNAL REFERENCE

Publication in progress.

XI. ACKNOWLEDGMENTS

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For a complete list of the Hematology Disease Site Group and the Practice Guidelines Coordinating Committee members, please visit the Cancer Care Ontario Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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